(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number
WO 2004/096212 A1

(51) International Patent Classification[7]: A61K 31/415, C07D 231/14, C07K 5/078, A61P 35/00

(21) International Application Number: PCT/GB2004/001740

(22) International Filing Date: 23 April 2004 (23.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0309637.7 28 April 2003 (28.04.2003) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

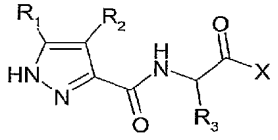
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/096212 A1

(54) Title: PYRAZOLE COMPOUNDS AS HSP90 INHIBITORS FOR THE TREATMENT OF CANCER



(I)

(57) Abstract: Compounds of formula (I) are inhibitors of HSP90 activity, and useful in the treatment of proliferative disease such as cancers: wherein R_1, R_2 and R_3 are as defined in the specification, and X is $-OR_4$ or $-NR_4R_5$ wherein R_4 and R_5 independently represent hydrogen or optionally substituted C_1-C_6 alkyl, or R_4 and R_5 taken together with the nitrogen to which they are attached form an optionally substituted nitrogen-containing ring having 5-8 ring atoms.

PYRAZOLE COMPOUNDS AS HSP90 INHIBITORS FOR THE TREATMENT OF CANCER

This invention relates to substituted pyrazoles having HSP90 inhibitory activity, to the use of such compounds in medicine, in relation to diseases which are mediated by excessive or inappropriate HSP90 activity such as cancers, and to pharmaceutical compositions containing such compounds.

Background to the invention

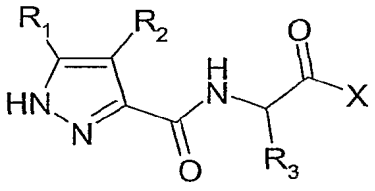
HSP90 (heat shock protein 90) is an ATP-dependent intracellular molecular chaperone. Due to its involvement in regulating a number of signalling pathways that are crucially important in driving the phenotype of a tumour, and the discovery that certain bioactive natural products exert their effects via HSP90 activity, the molecular chaperone HSP90 is currently regarded as a target for anticancer drug development.

Brief description of the invention

The present invention relates to the use of a class of substituted pyrazole compounds as HSP90 inhibitors, for example for inhibition of cancer cell proliferation. A core pyrazole ring with aromatic substitution on one ring carbon atom and a limited class of amido substitutents on another are principle characterising features of the compounds with which the invention is concerned.

Detailed Description of the Invention

The invention provides the use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of HSP90 activity:



(I)

wherein

R_1 is a group of formula (IA):

$$-Ar^1-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q \qquad (IA)$$

wherein in any compatible combination

Ar^1 is an optionally substituted aryl or heteroaryl radical,

Alk^1 and Alk^2 are optionally substituted divalent C_1-C_6 alkylene or C_2-C_6 alkenylene radicals,

p, r and s are independently 0 or 1,

Z is –O-, -S-, -(C=O)-, -(C=S)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^A-$, $-C(=S)NR^A-$, $-SO_2NR^A-$, $-NR^AC(=O)-$, $-NR^ASO_2-$ or $-NR^A-$ wherein R^A is hydrogen or C_1-C_6 alkyl, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical;

R_2 is (i) a group of formula (IA) as defined in relation to R_1;

(ii) a carboxamide radical; or

(iii) a non aromatic carbocyclic or heterocyclic ring wherein a ring carbon is optionally substituted, and/or a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ wherein Q, Alk^1, Alk^2, Z, p, r and s are as defined above in relation to group (IA); and

R_3 is hydrogen, or methyl, ethyl, n- or iso-propyl any of which being optionally substituted by hydroxy;

X is $-OR_4$ or $-NR_4R_5$ wherein R_4 and R_5 independently represent hydrogen or optionally substituted C_1-C_6 alkyl, or R_4 and R_5 taken together with the nitrogen to which they are attached form an optionally substituted nitrogen-containing ring having 5-8 ring atoms.

substrate 10 is then placed into a copper plating solution 18 for copper deposition. Figure 1B represents the instant when the substrate 10 is immersed into the plating solution 18, which is saturated with air or has a large concentration of dissolved gas. The plating is initiated by applying a potential between the conductive substrate surface (barrier layer 16 and/or seed layer 17) and an electrode (not shown) in the plating solution 18. Bubbles 20 represent the micro-bubbles that may initiate on the surface of the seed layer as soon as the wafer is placed in the solution. These bubbles may be micron or sub-micron in size and, they may be within the features 12, on the seed layer portion covering the top surface 13 or at the corners 21. As the plating continues, bubbles 20 retard material deposition onto the locations that they are attached and give rise to defects such as voids as depicted in Figure 1C. Also shown in Figure 1C is the possibility of having new bubbles 22 nucleate on surface 24 of the copper layer 26, which is being deposited. Figure 1D shows the substrate 10 after the copper deposition step is finished. As can be seen in Figure 1D, various defects 28 are created by the bubbles on the substrate surface either during the initial or later stages of the electrodeposition process. These defects, after the CMP and other process steps employed to fabricate the interconnect structure, cause reliability problems such as poor stress migration and poor electromigration. It should be noted that similar problems with bubbles are present for deposition of copper layers by the electroless deposition techniques.

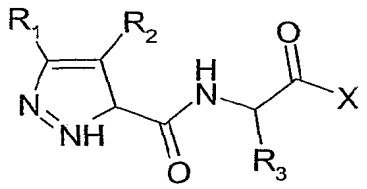
[0008] Formation of bubbles of gas on surfaces placed in plating electrolytes can cause other problems also. Even if bubbles are not formed on the wafer surface, they can form on other surfaces of the plating cell and then migrate to the wafer surface, giving rise to defects already described. In certain wet processing techniques, (such as electrochemical mechanical deposition and electrochemical mechanical polishing) there are pad structures or workpiece surface influencing device (WSID) structures proximate to the wafer surface. These pad structures are used to sweep the wafer surface during the electrochemical mechanical process to planarize or polish the wafer surface. The surfaces of all these structures, which are immersed in the process solutions and placed close to the wafer surface, are also possible sites for bubbles to initiate, grow and eventually migrate to the wafer surface causing defects.

SUMMARY

[0009] The problems described above can be resolved by using a degassed process solution or process electrolyte of the present invention. Degassing reduces dissolved gas content in the process solution and reduces the driving force for bubble formation on surfaces exposed to the degassed electrolyte.

In general, the class of compounds defined above in relation to formula (I) is believed to be novel, and the invention includes all novel members of that class and their salts, hydrates and solvates.

Structure (I) above is, of course, tautomeric with structure (I^1), and any reference herein to one tautomer include the other:



(I^1)

As used herein:

the term "carboxyl group" refers to a group of formula -COOH;

the term "carboxyl ester group" refers to a group of formula -COOR, wherein R is a radical actually or notionally derived from the hydroxyl compound ROH; and

the term " carboxamide group" refers to a group of formula $-CONR_aR_b$, wherein $-NR_aR_b$ is a primary or secondary (including cyclic) amino group actually or notionally derived from ammonia or the amine HNR_aR_b.

As used herein, the term "(C_1-C_6)alkyl" refers to a straight or branched chain alkyl radical having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C_1-C_6)alkylene radical" means a saturated hydrocarbon chain having from 1 to 6 carbon atoms and two unsatisfied valences.

As used herein, the term "(C_1-C_6)alkenyl" refers to a straight or branched chain alkenyl radical having from 2 to 6 carbon atoms and containing at least

one double bond of E or Z configuration, including for example, ethenyl and allyl.

As used herein the term "divalent (C_2-C_6)alkenylene radical" means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one double bond, and two unsatisfied valences.

As used herein, the term "(C_1-C_6)alkynyl" refers to a straight or branched chain alkenyl radical having from 2 to 6 carbon atoms and containing at least one triple bond, including for example, ethynyl and prop-2-ynyl.

As used herein the term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" refers to a carbocyclic radical having from 3-8 carbon atoms containing at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon, and includes monocyclic aryl, cycloalkyl and cycloalkenyl radicals.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent selected from, for example, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$, -$NR^BSO_2OR^A$, -$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group. The term "optional substituent" refers to one of the foregoing substituent groups.

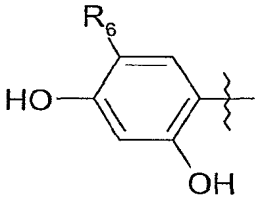
As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or

phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

Some compounds of the invention contain one or more actual or potential chiral centres because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

The radical R_1

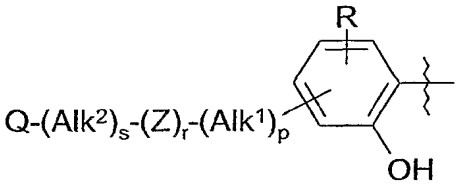
In one embodiment of the invention, R_1 has formula (IB):



(IB)

wherein R_6 is chloro, bromo, C_1-C_6 alkyl, or cyano.

In another embodiment R_1 has formula (IC):



(IC)

wherein Alk^1, Alk^2, p, r, s, Z and Q are as defined in claim 1 in relation to formula (IA), and R represents one or more optional substituents. In such cases it is currently preferred that R is –OH in the 4- position of the phenyl ring and the $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ substituent is in the 5- position of the phenyl ring. In one class of structures of type (IC), r is 0, and Q is hydrogen or optionally substituted phenyl, and in those cases s may be 0, p may be 1 and Alk^1 may be a non-substituted divalent C_1-C_6 alkylene or C_2-C_6 alkenylene radical, for example $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or –CH=CH-. In another class of structures of type (IC), p, r and s may each be 0 and Q may be optionally substituted phenyl.

The radical R_2

When R_2 is of type (i), i.e. a group of formula (IA), examples include phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-furanyl, 2- or 3-thienyl, and thiazolyl wherein optional substituents include any of those listed above in the definition of "substituted", for example methoxy , ethoxy methylenedioxy, ethylenedioxy, fluoro, chloro, bromo, and trifluoromethyl. Currently preferred are compounds wherein R_2 is phenyl substituted in the 4 position by C_1-C_6 alkoxy such as methoxy or ethoxy, fluoro, chloro, bromo, morpholinomethyl, piperazino, N-methylpiperazino, or piperidino. Also preferred are compounds wherein R_2 is phenyl substituted in the 4 position by optionally substituted C_{1-6} alkyl, eg optionally substituted methyl, ethyl, n-propyl or iso-propyl. Additionally preferred are compounds wherein R_2 is phenyl substituted in the 4 position by optionally substituted morpholino C_{1-6} alkyl-, thiomorpholino C_{1-6} alkyl-, piperazino C_{1-6} alkyl-, methyl piperazino C_{1-6} alkyl-, or diethylamino. Further preferred are compounds wherein R_2 is phenyl substituted in the 4 position by $-NH_2$, $-NHR^A$, $-NR^AR^B$, $-NHCOR^A$, $-NHCOOR^A$, $-NR^BCOOR^A$, $-NHSO_2OR^A$, $-NR^BSO_2OR^A$, $-NHCONH_2$, $-NR^ACONH_2$, $-NHCONHR^B$, $-NR^ACONHR^B$, $-NHCONR^AR^B$, or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group. Still further preferred are compounds wherein R_2 is phenyl substituted in the 4 position by optionally substituted piperadino, piperazino, morpholino or thiomorpholino.

When R_2 is a carboxamide radical of type (ii) above, examples include those of formula $-CONR^B(Alk)_nR^A$ wherein

Alk is a divalent alkylene, alkenylene or alkynylene radical, for example a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH=CH-$, or $-CH_2CCCH_2-$ radical, and the Alk radical may be optionally substituted,

n is 0 or 1,

R^B is hydrogen or a C_1-C_6 alkyl or C_2-C_6 alkenyl group, for example methyl, ethyl, n- or iso-propyl, or allyl,

R^A is hydroxy or optionally substituted carbocyclic, for example hydroxy and/or chloro-substituted phenyl and 3,4 methylenedioxyphenyl; or heterocyclyl, for example pyridyl, furyl, thienyl, N-piperazinyl, or N-morpholinyl any of which heterocyclic rings may be substituted,

or R^A and R^B taken together with the nitrogen to which they are attached form an N-heterocyclic ring which may optionally contain one or more additional hetero atoms selected from O, S and N, and which may optionally be substituted on one or more ring C or N atoms, examples of such N-heterocyclic rings including morpholino, piperidinyl, piperazinyl and N-phenylpiperazinyl.

The group R_3

Presently it is preferred that R_3 be hydrogen or methyl. Preferably also, when R_3 is other than hydrogen the stereochemical configuration at the carbon centre to which it is attached is that of a D amino acid.

The group X

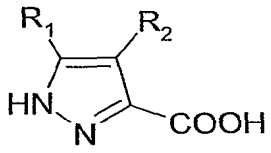
In one preferred class of compounds with which the invention is concerned, X is $-OR_4$ or $-NHR_4$ wherein R_4 is C_1-C_6 alkyl, optionally substituted by hydroxy, or a primary- secondary, tertiary- or cyclic-amino group such as a morpholino, piperidinyl or piperazinyl group, the latter being optionally substituted by C_1-C_6 alkyl on the second nitrogen.

In another preferred class, X is $-NR_4R_5$ wherein R_4 and R_5 taken together with the nitrogen to which they are attached form a morpholino, piperidinyl or piperazinyl ring, the latter being optionally substituted by C_1-C_6 alkyl on the second nitrogen.

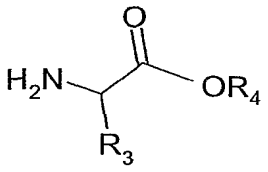
Specific compounds with which the invention is concerned include those of the Examples.

Compounds with which the invention is concerned may be prepared by literature methods, such as those of the preparative Examples herein, and methods analogous thereto.

Thus, compounds of formula (I) wherein X is $-OR_4$ may be prepared by coupling a carboxylic acid of formula (II) with an amino acid of formula (III)



(II)



(III)

Compounds of formula (I) wherein X is –OH may be prepared by hydrolysis of the ester compound (III). Those compounds may be condensed with the amine HNR_4R_5 to prepare compounds of formula (I) wherein X is $-NR_4R_5$.

The compounds of the invention are inhibitors of HSP90 and are thus useful in the treatment of diseases which are mediated by excessive or inappropriate HSP90 activity such as cancers; viral diseases such as Hepatitis C (HCV) (Waxman, 2002); Immunosupression such as in transplantation (Bijlmakers, 2000 and Yorgin, 2000); Anti-inflammatory diseases (Bucci, 2000) such as Rheumatoid arthritis, Asthma, MS, Type I Diabetes, Lupus, Psoriasis and Inflammatory Bowel Disease; Cystic fibrosis (Fuller, 2000); Angiogenesis-related diseases (Hur, 2002 and Kurebayashi, 2001): diabetic retinopathy, haemangiomas, psoriasis, endometriosis and tumour angiogenesis. Also an Hsp90 inhibitor of the invention may protect normal cells against chemotherapy-induced toxicity and be useful in diseases where failure to undergo apoptosis is an underlying factor. Such an Hsp90 inhibitor may also be useful in diseases where the induction of a cell stress or heat shock protein response could be beneficial, for example, protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart (Hutter, 1996 and Trost, 1998) and brain (Plumier, 1997 and Rajder, 2000). An Hsp90 inhibitor could also be useful in diseases where protein misfolding or aggregation is a major causal factor , for example, scrapie/CJD, Huntingdon's and Alzheimer's (Sittler, 2001; Trazelt, 1995 and Winklhofer, 2001).

Accordingly, the invention also provides:

(i) a method of treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity in mammals, particularly humans, which method comprises administering to the mammal an amount of a compound of formula (I) as defined above, or a salt, hydrate or solvate thereof, effective to inhibit said HSP90 activity.; and

(ii) a compound of formula (I) as defined above, or a salt hydrate or solvate thereof, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity;

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting

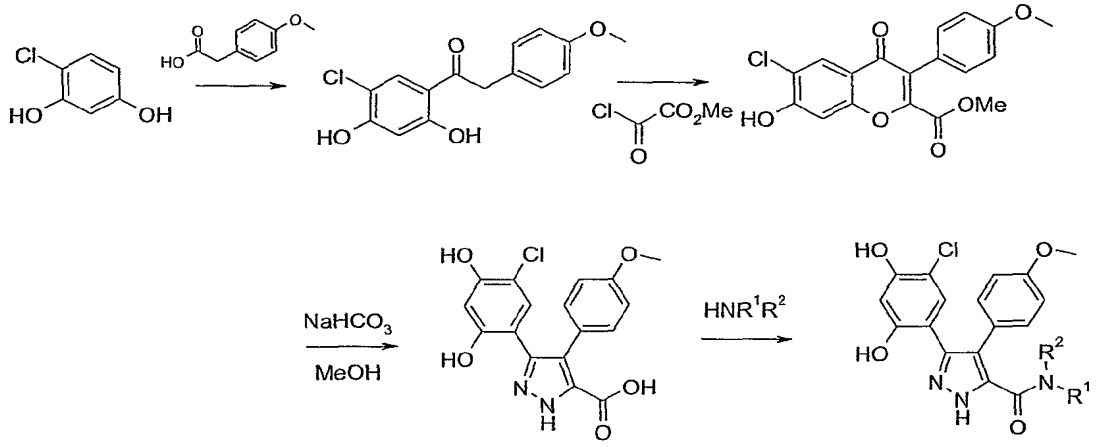
lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

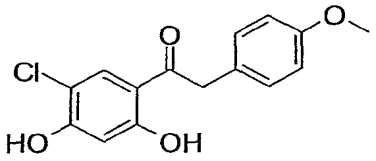
The following examples illustrate the preparation and activities of specific compounds of the invention.

Experimental Section



Scheme 1: General scheme for preparation of 5-amides

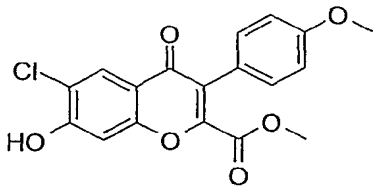
1-(5-Chloro-2,4-dihydroxy-phenyl)-2-(4-methoxy-phenyl)-ethanone



4-Chlororesorcinol (1eq) and *para*-methoxyphenylacetic acid (1eq) were combined in boron trifluoride.diethyletherate (5eq) and heated to 90°C under nitrogen for 3 hours. The reaction was allowed to cool to room temperature and was then added drop wise to 10% NaOAc (aq). The mixture was allowed to stand overnight, and the subsequent solid was collected by vacuum filtration. The solid was dried under vacuum to give 1-(5-chloro-2,4-dihydroxy-phenyl)-2-(4-methoxy-phenyl)-ethanone.

LC/MS retention time 2.485 minutes $[M+H]^+$ 293.2/295.2 chlorine splitting pattern.

6-Chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid methyl ester



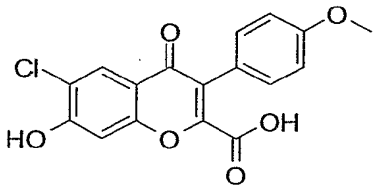
1-(5-Chloro-2,4-dihydroxy-phenyl)-2-(4-methoxy-phenyl)-ethanone (1eq) was taken up in anhydrous pyridine and cooled on an ice bath to 0°C. Methyl chlorooxoacetate (3eq) was added dropwise and the solution was stoppered and allowed to stand in the refrigerator over night.

The bright orange solution was added carefully to 100ml 1M HCl (aq) and extracted into 2x70ml DCM. The organic phases were combined and washed with 2x50ml brine. All was concentrated in vacuo to a yellow solid. This was suspended in a 1:1 mixture of 1MHCl (aq) and methanol. All was heated at reflux for 4hrs. Allowed to cool.

The reaction mixture was concentrated *in vacuo* to give 6-chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid methyl ester as a pale yellow solid

LC retention time 2.423minutes $[M+H]^+$ 361.2/363.2 chlorine splitting pattern.

6-Chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid

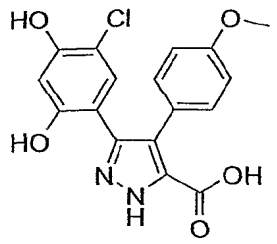


6-Chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid methyl ester was taken up in a 2:1 mixture of sat. $NaHCO_3$ (aq): Methanol and all was heated at 65°C for 5 hours. The solution was cooled to room temperature and concentrated in vacuo to remove the methanol. The residual aqueous solution was acidified with 1M HCl (aq) and a buff coloured precipitated dropped out of solution. This was collected by vacuum filtration, washed with water and with diethyl ether, to give 6-chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid

.

LC retention time 1.814 minutes 347.2/349.2 chlorine splitting pattern.

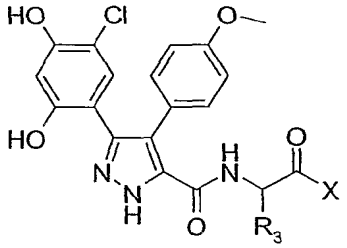
5-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-methoxy-phenyl)-2H-pyrazole-3-carboxylic acid



6-Chloro-7-hydroxy-3-(4-methoxy-phenyl)-4-oxo-4H-chromene-2-carboxylic acid (1eq) was taken up in ethanol and hydrazine hydrate (3eq) was added. To aid dissolution a few drops of NaHCO3 (aq) was added, and then all was heated at 70°C under nitrogen for 2 hours. The solution was cooled to room temperature and concentrated in vacuo to a brown oil. This was partitioned between 1MHCl(aq) and diethyl ether. The organic phases were combined, washed with 1MHCl(aq), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 5-(5-chloro-2,4-dihydroxy-phenyl)-4-(4-methoxy-phenyl)-2H-pyrazole-3-carboxylic acid as a yellow foam.

LC retention time 2.020min $[M+H]^+$ 361.2/ 363.2 chlorine splitting pattern.

General Synthesis of Amides



Method 1

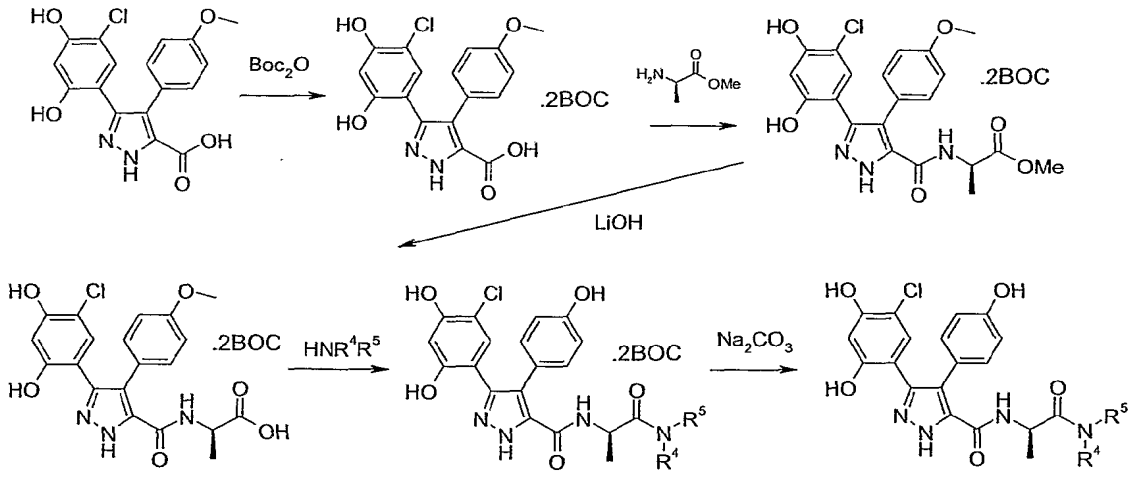
5-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-methoxy-phenyl)-2H-pyrazole-3-carboxylic acid (1eq) was taken up as a suspension in anhydrous dichloromethane. The resulting solution was cooled to 0°C under nitrogen. 1-hydroxybenzotriazole hydrate (3eq) was added, followed by N-methylmorpholine (10eq), N-Ethyl-N'-(3dimethylaminopropyl)carbodiimide.HCl (3eq) and amine (2eq). All was stirred to room temperature overnight. The resulting solutions were diluted with dichloromethane and extracted with 1MHCl(aq), sat. $NaHCO_3$ (aq) and sat. NaCl (aq), then dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The residue was purified by preparative LC/MS to give the amide product.

Method 2

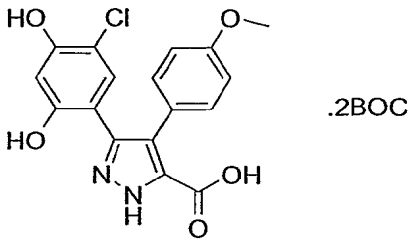
The acid (1eq) was taken up in anhydrous dichloromethane and the solution was cooled to 0°C under nitrogen. Triethylamine (6eq) was added, followed by 4-(dimethylamino)pyridine (0.5eq). Di-tert-butyl dicarbonate (3eq) as a solution in anhydrous dichloromethane was added drop wise over a period of 30 minutes followed by the amine (2eq). The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was washed with 1MHCl (aq) and then brine, and dried over $MgSO_4$. The solution was filtered and concentrated in *vacuo*.

The gum was dissolved in methanol. Excess 1M Na_2CO_3 (aq) was added and the solution was heated to 80°C under nitrogen for 8 hours, then allowed to cool back to room temperature. The residue was purified by preparative LC/MS.



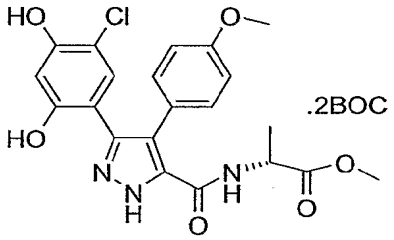
Scheme 2: 5-position extended amide synthesis

Method 3



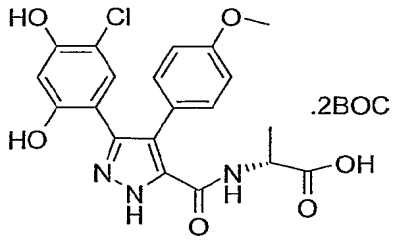
The acid (1eq) was taken up in anhydrous dichloromethane and the solution was cooled to 0°C under nitrogen. Triethylamine (6eq) was added, followed by 4-(dimethylamino)pyridine (0.5eq). Di-tert-butyl dicarbonate (3eq) as a solution in anhydrous dichloromethane was added drop wise over a period of 30 minutes. The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was washed with 1MHCl (aq) and then brine, and dried over $MgSO_4$. The solution was filtered and concentrated in *vacuo*.

LC/MS retention time 2.86min $[M\text{-}Boc]^+$ 505.4/507.4 chlorine splitting pattern.



The carboxylic acid (1eq) was dissolved in anhydrous dichloromethane. The resulting solution was cooled to 0°C under nitrogen. 1-hydroxybenzotriazole hydrate (3eq) was added, followed by N-methylmorpholine (8eq), N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide.HCl (3eq) and H-D-ALA-OMe.HCl (2eq). All was stirred to room temperature overnight. The resulting solutions were diluted with dichloromethane and extracted with 1MHCl(aq), sat. $NaHCO_3$ (aq) and sat. NaCl (aq), then dried over $MgSO_4$, filtered and concentrated in *vacuo* and purified by flash chromatography (eluting with 1% MeOH-DCM).

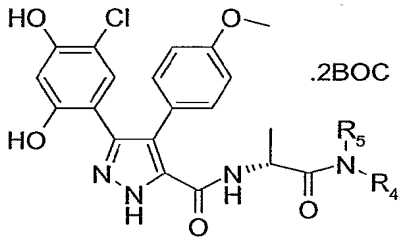
LC/MS retention time 2.97min $[M+H]^+$646.5/648.5 chlorine splitting pattern.



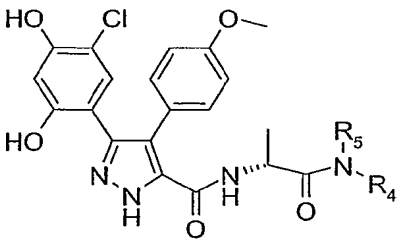
The ester (1eq) was taken up in a 1:1 solution of water:1,4-dioxan. 1M LiOH (aq) was added and all was stirred at room temperature for 90 minutes under nitrogen.

The reaction mixture was diluted with water and washed with diethyl ether. The aqueous phase was acidified with 1M HCl (aq) and extracted into dichloromethane. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo to give the carboxylic acid as a foam.

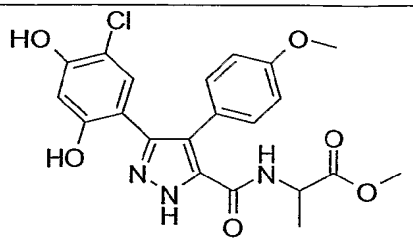
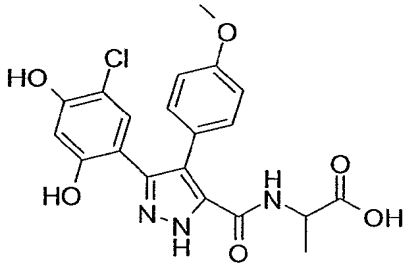
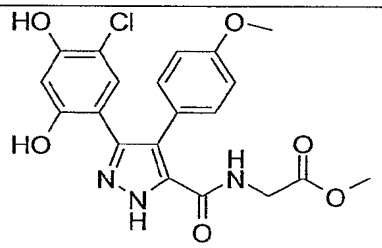
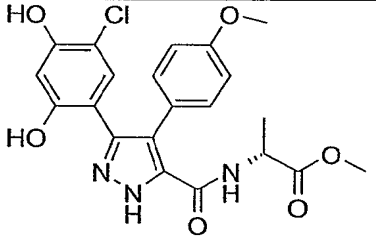
LC/MS retention time 2.851 min 632.5/634.5

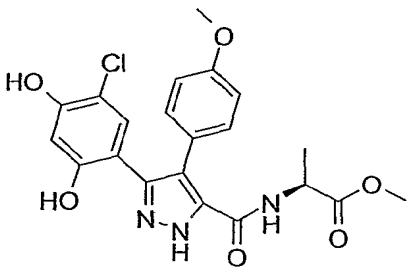
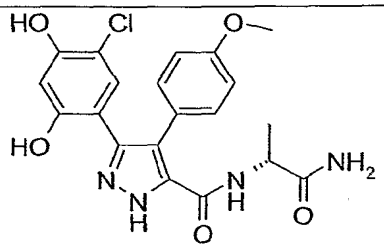
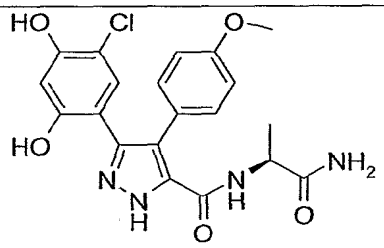
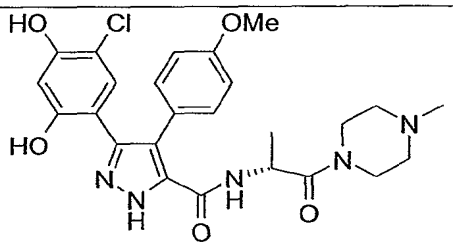
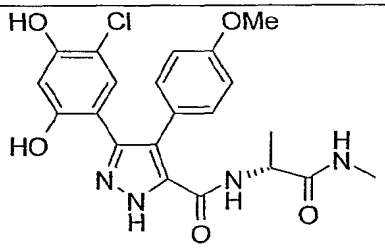
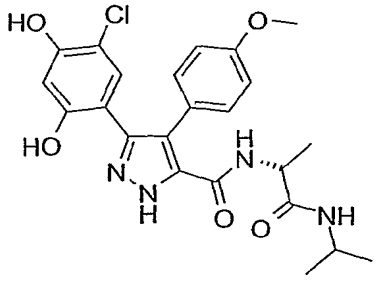


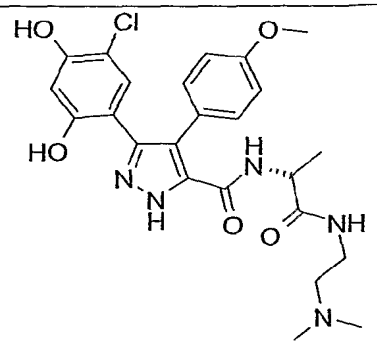
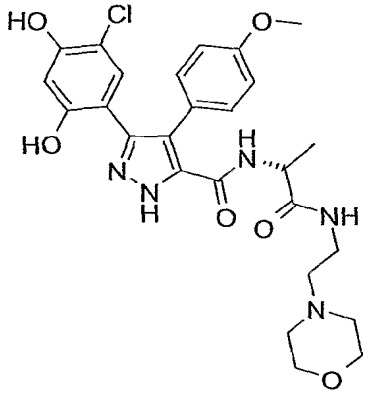
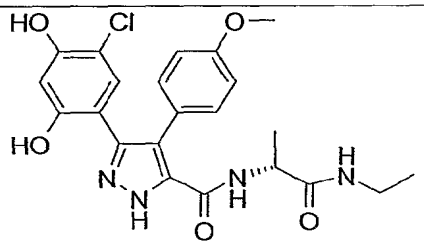
The carboxylic acid (1eq) was dissolved in anhydrous dichloromethane. The resulting solution was cooled to 0°C under nitrogen. 1-hydroxybenzotriazole hydrate (3eq) was added, followed by N-methylmorpholine (8eq), N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide.HCl (3eq) and amine (2eq). All was stirred to room temperature overnight. The resulting solutions were diluted with dichloromethane and extracted with 1MHCl(aq), sat. $NaHCO_3$ (aq) and sat. NaCl (aq), then dried over $MgSO_4$, filtered and concentrated in vacuo and purified by flash chromatography (eluting with 1% MeOH-DCM).



The gum was dissolved in methanol. Excess 1M Na_2CO_3 (aq) was added and the solution was heated to 80°C under nitrogen for 8 hours, then allowed to cool back to room temperature. The residue was purified by preparative LC/MS.

Example	Structure	MH+	Synthetic Comment	Hsp90 FP IC_{50}§
3		445 447	Rac-Ala-methyl ester .HCl by Method 1	A
4		432 434	Saponification of Example 3 at room temperature in 6:1 MeOH : 5%NaOH (aq)	A
6		432 434	Glycine methyl ester.HCl by Method 1	A
7		446 448	H-D-ALA-OMe.HCl by Method 1	A

8		446 448	H-ALA-OMe.HCl by Method 1	A
9		431 433	H-D-ALA-NH_2.HCl by Method 1	A
10		431 433	H-ALA-NH_2.HCl by Method 1	A
12		514 516	Methyl piperazine by Method 3	A
13		445 447	Methyl amine by Method 3	A
14		473 775	Isopropylamine by Method 3	A

15		502 504	Dimethylamino ethylamine by Method 3	A
16		544 546	Morpholino- N-ethylamine by Method 3	A
18		459 461	Ethylamine by Method 3	A

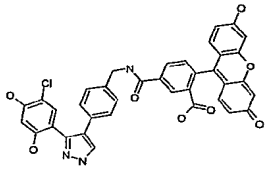
§ 'A' = IC50 <10uM in the Fluorescence Polarisation Assay described below:

Fluorescence Polarization Assay

Fluorescence polarization {also known as fluorescence anisotropy} measures the rotation of a fluorescing species in solution, where the larger molecule the more polarized the fluorescence emission. When the fluorophore is excited with polarized light, the emitted light is also polarized. The molecular size is proportional to the the polarization of the fluorescence emission.

The fluoroscein-labelled probe – RBT0045864-FAM - binds to HSP90 { full-length human, full-length yeast or N-terminal domain HSP90 } and the anisotropy {rotation of the probe-protein complex} is measured.

Compound is added to the assay plate, left to equilibrate and the anisotropy measured again. Any change in anisotropy is due to competitive binding of compound to HSP90, thereby releasing probe.



RBT0045864-FAM

Materials

Chemicals are of the highest purity commercially available and all aqueous solutions are made up in AR water.

1) Costar 96-well black assay plate #3915
2) Assay buffer of (a)100mM Tris pH7.4; (b) 20mM KCl; (c) 6mM $MgCl_2$. Stored at room temperature.
3) BSA (bovine serum albumen) 10 mg/ml (New England Biolabs # B9001S)
4) 20 mM RBT0045864 (pyrazole) in 100 % DMSO stock concentration. Stored in the dark at RT. Made in-house, K_d ~ 200 µM, depending on the protein used. Working concentration is 200 nM diluted in AR water and stored at 4 °C. Final concentration in assay 80 nM.
5) E. coli expressed human full-length HSP90 protein, purified >95% (see, e.g., Panaretou et al., EMBO J., Vol. 17, pp. 4829-4836, 1998) and stored in 50µL aliquots at -80°C .

Protocol

1) Add 100µl 1x buffer to wells 11A and 12A (=FP BLNK)

2) Prepare assay mix – all reagents are kept on ice with a lid on the bucket as the probe is light-sensitive.

	i.	Final Conc^{n}
• 1x Hsp90 FP Buffer	10 ml	1x
• BSA 10mg/ml (NEB)	5.0 µl	5 µg/ml
• Probe 200µM	4.0 µl	80 nM
• Human full-length Hsp90	6.25 µl	200 nM

3) Aliquot 100µl assay mix to all other wells
4) Seal plate and leave in dark at room temp for 20 minutes to equilibrate

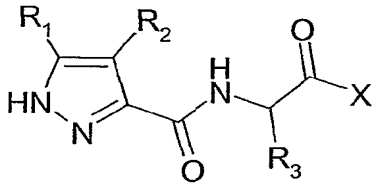
Compound Dilution Plate – 1 x 3 dilution series

1) In a clear 96-well v-bottom plate – {# VWR 007/008/257} add 10 µl 100% DMSO to wells B1 to H11
2) To wells A1 to A11 add 17.5µl 100% DMSO
3) Add 2.5 µl cpd to A1. This gives 2.5 mM {50x} stock cpd – assuming cpds 20 mM.
4) Repeat for wells A2 to A10. Control in columns 11 and 12.
5) Transfer 5 µl from row A to row B- not column 12. Mix well.
6) Transfer 5 µl from row B to row C. Mix well.
7) Repeat to row G.
8) Do not add any compound to row H – this is the 0 row.
9) This produces a 1x3 dilution series from 50 µM to 0.07 µM.
10) In well B12 prepare 20 µl of 100 µM standard compound.
11) After first incubation the assay plate is read on a Fusion™ a-FP plate reader (Packard BioScience, Pangbourne, Berkshire,UK).
12) After the first read, 2 µl of diluted compound is added to each well for columns 1 to 10. In column 11 {provides standard curve} only add compound B11 – H11. Add 2 µl of 100mM standard cpd to wells B12 – H12 {is positive control }

The Z' factor is calculated from zero controls and positive wells. It typically gives a value of 0.7 – 0.9.

Claims:

1. The use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of HSP90 activity:



(I)

wherein

R_1 is a group of formula (IA):

$$-Ar^1-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q \qquad (IA)$$

wherein in any compatible combination

Ar^1 is an optionally substituted aryl or heteroaryl radical,

Alk^1 and Alk^2 are optionally substituted divalent C_1-C_6 alkylene or C_2-C_6 alkenylene radicals,

p, r and s are independently 0 or 1,

Z is –O-, -S-, -(C=O)-, -(C=S)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^A-$, $-C(=S)NR^A-$, $-SO_2NR^A-$, $-NR^AC(=O)-$, $-NR^ASO_2-$ or $-NR^A-$ wherein R^A is hydrogen or C_1-C_6 alkyl, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical;

R_2 is (i) a group of formula (IA) as defined in relation to R_1;

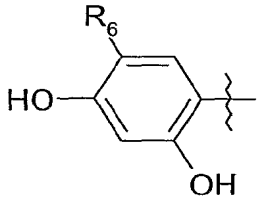
(ii) a carboxamide radical; or

(iii) a non aromatic carbocyclic or heterocyclic ring wherein a ring carbon is optionally substituted, and/or a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ wherein Q, Alk^1, Alk^2, Z, p, r and s are as defined above in relation to group (IA); and

R_3 is hydrogen, or methyl, ethyl, n- or iso-propyl any of which being optionally substituted by hydroxy;

X is $-OR_4$ or $-NR_4R_5$ wherein R_4 and R_5 independently represent hydrogen or optionally substituted C_1-C_6 alkyl, or R_4 and R_5 taken together with the nitrogen to which they are attached form an optionally substituted nitrogen-containing ring having 5-8 ring atoms.

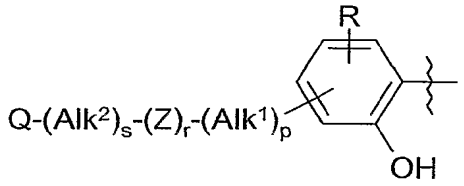
2. The use as claimed in claim 1 wherein in the compound of formula (I), R_1 has formula (IB):



(IB)

wherein R_6 is chloro, bromo, C_1-C_6 alkyl, or cyano.

3. The use as claimed in claim 1 wherein in the compound of formula (I) R_1 has formula (IC):



(IC)

wherein Alk^1, Alk^2, p, r, s, Z and Q are as defined in claim 1 in relation to formula (IA), and R represents one or more optional substituents.

4. The use as claimed in claim 2 wherein R is –OH in the 4- position of the phenyl ring and the $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ substituent is in the 5- position of the phenyl ring.

5. The use as claimed in claim 4 wherein r is 0, and Q is hydrogen or optionally substituted phenyl.

6. The use as claimed in claim 5 wherein s is 0, p is 1 and Alk^1 is a non-substituted divalent C_1-C_6 alkylene or C_2-C_6 alkenylene radical.

7. The use as claimed in claim 5 wherein Alk^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH=CH-$.

8. The use as claimed in claim 4 wherein p, r and s are each 0

9. The use as claimed in any of the preceding claims wherein R_2 is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-furanyl, 2- or 3-thienyl, or thiazolyl, optionally substituted by one or more of methoxy, ethoxy, methylenedioxy, ethylenedioxy, fluoro, chloro, bromo, or trifluoromethyl.

10. The use as claimed in any of claims 1 to 8 wherein R_2 is optionally substituted phenyl.

11 The use as claimed in any of claims 1 to 8 wherein R_2 is phenyl substituted in the 4 position by (i) C_1-C_6 alkoxy such as methoxy or ethoxy, fluoro, chloro, bromo, morpholinomethyl, piperazino, N-methylpiperazino, or piperidino, (ii)optionally substituted C_{1-6} alkyl, eg optionally substituted methyl, ethyl, n-propyl or iso-propyl (iii) optionally substituted morpholino C_{1-6} alkyl-, thiomorpholino C_{1-6} alkyl-, piperazino C_{1-6} alkyl-, methyl piperazino C_{1-6} alkyl-, or diethylamino (iv) $-NH_2$, $-NHR^A$, $-NR^AR^B$, $-NHCOR^A$, $-NHCOOR^A$, $-NR^BCOOR^A$, $-NHSO_2OR^A$, $-NR^BSO_2OR^A$, $-NHCONH_2$, $-NR^ACONH_2$, $-NHCONHR^B$, $-NR^ACONHR^B$, $-NHCONR^AR^B$, or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group or (v) optionally substituted piperadino, piperazino, morpholino or thiomorpholino.

12. The use as claimed in any of claims 1 to 8 wherein R_2 is a carboxamide radical of formula $-CONR^B(Alk)_nR^A$ wherein

Alk is an optionally substituted divalent alkylene, alkenylene or alkynylene radical,

n is 0 or 1,

R^B is hydrogen or a C_1-C_6 alkyl or C_2-C_6 alkenyl group,

R^A is hydroxy or an optionally substituted carbocyclic or heterocyclic ring,

or R^A and R^B taken together with the nitrogen to which they are attached form an N-heterocyclic ring which may optionally contain one or more additional hetero atoms selected from O, S and N, and which may optionally be substituted on one or more ring C or N atoms.

13. The use as claimed claim 12 wherein

Alk is an optionally substituted $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH=CH-$, or $-CH_2CCCH_2-$ radical.

n is 0 or 1,

R^B is hydrogen, methyl, ethyl, n- or iso-propyl, or allyl,

R^A is hydroxy, hydroxy and/or chloro-substituted phenyl, 3,4 methylenedioxyphenyl, pyridyl, furyl, thienyl, N-piperazinyl, or N-morpholinyl,

or R^A and R^B taken together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl or N-phenylpiperazinyl ring.

14. The use as claimed in claim 12 wherein n is 0, R^B is hydrogen and R^A is hydroxy or an optionally substituted carbocyclic or heterocyclic ring.

15. The use as claimed in any of the preceding claims wherein R_3 is hydrogen.

16. The use as claimed in any of claims 1 to 14 wherein R_3 is other than hydrogen and the stereochemical configuration at the carbon centre to which it is attached is that of a D amino acid.

17. The use as claimed in any of the preceding claims wherein X is $-OR_4$ or $-NHR_4$ wherein R_4 is C_1-C_6 alkyl, optionally substituted by hydroxy, or a primary- secondary, tertiary- or cyclic-amino group

18. The use as claimed in any of the preceding claims wherein X is $-NR_4R_5$ wherein R_4 and R_5 taken together with the nitrogen to which they are attached form a morpholino, piperidinyl or piperazinyl ring, the latter being optionally substituted by C_1-C_6 alkyl on the second nitrogen.

19. A method of treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity in mammals which method comprises administering to the mammal an amount of a compound of formula (I) as defined in any of claims 1 to 15, or a salt, hydrate or solvate thereof, effective to inhibit said HSP90 activity.

20. The use as claimed in any of claims 1 to 18 or a method as claimed claim 16 for immunosupression or the treatment of cancer; viral disease, inflammatory diseases such as rheumatoid arthritis, asthma, multiple sclerosis, Type I diabetes, lupus, psoriasis and inflammatory bowel disease; cystic fibrosis angiogenesis-related disease such as diabetic retinopathy, haemangiomas, and endometriosis; or for protection of normal cells against chemotherapy-induced toxicity; or diseases where failure to undergo apoptosis is an underlying factor; or protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart and brain; scrapie/CJD, Huntingdon's and Alzheimer's disease.

21. A compound of formula (I) as defined in any of claims 1 to 18, or a salt hydrate or solvate thereof, for use in human or veterinary medicine.

22. A compound of formula (I) as defined in any of claims 1 to 18, or a salt, solvate or hydrate thereof.

23. A compound whose structure is set forth in any of the Examples herein, or a salt, solvate or hydrate thereof.

24. A pharmaceutical or veterinary composition comprising a compound as defined in claim 22 or claim 23, together with a pharmaceutically or veterinarily acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001740

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 C07D231/14 C07K5/078 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/36075 A (SLOAN KETTERING INST CANCER ; ROSEN NEAL (US); CHIOSIS GABRIELA (US)) 10 May 2002 (2002-05-10) the whole document	1-24
P,X	WO 03/055860 A (CANCER RES TECHNOLOGY LTD ; DRYSDALE MARTIN JAMES (GB); PEARL LAURENCE) 10 July 2003 (2003-07-10) page 36, line 8 - line 16; claim 1 page 90, line 23 - page 91, line 2 page 112, line 11 - line 13 page 232, line 12 - page 235, line 4	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2004	26/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seymour, L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/001740

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB2004/001740

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0236075 A	10-05-2002	AU 2877102 A	15-05-2002
		CA 2426952 A1	10-05-2002
		EP 1335920 A2	20-08-2003
		JP 2004514660 T	20-05-2004
		WO 0236075 A2	10-05-2002
WO 03055860 A	10-07-2003	WO 03055860 A1	10-07-2003